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(54) FORME GALENIQUE TRANSCUTANEE POUR LE TRAITEMENT DU SYNDROME DES JAMBES SANS REPOS

(54) TRANS-EPICUTANEOUS ADMINISTRATION FORM FOR TREATING RESTLESS LEG SYNDROME

(57)

The invention relates to a trans-epicutaneous pharmaceutical composition containing Rotigotin for effective treatment of Restless Leg Syndrome (RLS), especially in the form of a transdermal therapeutic system (TDS) based on acrylate or silicone having a surface of 2.5 - 20 cm2 and containing 1.125 9.0 mg/cm2 Rotigotin as an active component against Restless Leg Syndrome, which, according to the International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, results in an improvement in the conditions of human Restless Leg Syndrome patients in comparison with a placebo treatment of 2 units or more, after administration over a period of time of at least 8 days.

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(54) Title: TRANS-EPICUTANEOUS ADMINISTRATION FORM FOR TREATING RESTLESS LEG SYNDROME

(57) Abrégé/Abstract:
The invention relates to a trans-epicutaneous pharmaceutical composition containing Rotigotin for effective treatment of Restless Leg Syndrome (RLS), especially in the form of a transdermal therapeutic system (TDS) based on acrylate or silicone having a surface of 2.5 - 20 cm^2 and containing 1.125 9.0 mg/cm^2 Rotigotin as an active component against Restless Leg Syndrome, which, according to the International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, results in an improvement in the conditions of human Restless Leg Syndrome patients in comparison with a placebo treatment of 2 units or more, after administration over a period of time of at least 8 days.

ABSTRACT

The invention relates to a trans-epicutaneous pharmaceutical composition containing Rotigotin for effective treatment of Restless Leg Syndrome (RLS), especially in the form of a transdermal therapeutic system (TDS) based on acrylate or silicone having a surface of 2.5 - 20 cm2 and containing 1.125 9.0 mg/cm2 Rotigotin as an active component against Restless Leg Syndrome, which, according to the International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, results in an improvement in the conditions of human Restless Leg Syndrome patients in comparison with a placebo treatment of 2 units or more, after administration over a period of time of at least 8 days.

Transepicutaneous Administration Form for Treating Restless Leg Syndrome

The invention relates to the use of rotigotine for the production of a medicament in a transepicutaneous application form, in particular in the form of a transdermal therapeutic system (TDS), for the treatment of Restless Leg Syndrome.

Background of the Invention

Restless Leg Syndrome, hereinafter also referred to as RLS, is a neurological disorder and manifests itself as paraesthesia in the legs accompanied by a strong urge to move. RLS manifests itself as prickling, tugging, pulling, itching, burning, cramps or pains and causes a compelling urge to move in the affected persons. These complaints frequently occur when the affected person is resting.

These sensory disorders and the resulting urge to move lead to restlessness and sleep disturbances particularly at night when falling asleep and during nocturnal sleep.

RLS can occur at all ages, however it occurs more frequently with increased age. Prevalence in the general population is approximately 10%. Owing to the nature of the symptoms, RLS is one of the most frequent causes of sleep disturbances. RLS is the cause of sleep/wake disorders in 5 % of 20 to 40 year olds, in 20 % of 40 to 60 year olds and in 35% of over sixty year olds.

If the patients' quality of sleep or quality of life becomes increasingly limited by RLS or if patients suffer from tiredness during the day, this is an indication that a therapy is appropriate. The need for therapy generally occurs at the age of 40 to 50 years old.

In therapy studies, monotherapies using dopamine agonists, opiates, benzodiazepines, carbamazepine, clonidine or levodopa (L-DOPA) in combination with a dopa decarboxylase inhibitor had different successes.

The use of L-DOPA for RLS was examined most frequently. There was a clear decrease in complaints in a long-term therapy with L-DOPA and the quality of life and sleep improved. The disadvantage of the therapy, however, is that the effect only lasts for a short time in a number of patients owing to the short half-life of L-DOPA. Long-term use furthermore leads to a decrease in effect (development of tolerance) and/or to a shifting of

the RLS complaints to the morning (rebound) or to a worsening of the complaints, with disorders also occurring during the day (augmentation).

Augmentation, rebound and tolerance are described in detail as follows for RLS:

a) Augmentation

In patients with RLS, augmentation includes

- the occurrence of RLS symptoms earlier in the evening than was the case before treatment;
- the occurrence of symptoms during the day;
- the affection of other body parts, typically the arms;

or

- a more rapid progression of the symptoms than in untreated cases.

One form of augmentation in particular in RLS patients is undesirable. It is described as an increase in the severity of the RLS complaints during the day, followed by a reduction in symptoms at night if the medicament is respectively taken in the evening.

b) Rebound

This phenomenon is similar to augmentation and manifests itself in particular as the occurrence of RLS symptoms in the morning, shortly after waking when the level of effect is subsiding.

c) Tolerance

This can be described in RLS patients as adaptation to an active substance-based therapy.

It manifests itself in that either ever-increasing doses of active substance have to be administered to the patient in order to alleviate the same symptoms of RLS or that

the same amount of active substance does not alleviate the complaints to the same extent as was the case at the beginning of the therapy.

Further individual dopamine agonists were examined as regards their therapeutic applicability in short-term therapy studies. Amongst the examined dopamine agonists were: bromocriptine, cabergoline, alpha dihydroergocryptine, lisuride, pergolide, pramipexole and ropinirole. It was found that all of these dopamine agonists are effective, however they have the disadvantage that they cause side effects such as nausea, vomiting, dizziness, hypotonia, constipation and insomnia, which generally occur at the beginning and depending on the dose.

Benzodiazepines and opiates are also used for RLS. However, owing to the danger of addiction and development of tolerance, these substances are only restrictedly available for a therapy.

The effect of transdermally administered clonidine, 2-(2,6-dichloroanilino)-4,5-dihydroimidazole, which was originally developed as an antihypertensive and miotic agent, was examined for the treatment of RLS. It was thereby found that although sleep onset latency was reduced, the quality of sleep, the frequency of waking and periodic leg movements during sleep (PLMS) were, on the other hand, not influenced. Since more effective substances are available as a monotherapy, clonidine is currently only restrictedly recommended as an alternative form of therapy.

Most of the current monotherapies, for example therapy with L-dopa, have the disadvantage that the amount of corresponding active substance has to be increased depending on the duration of the therapy in order to ensure therapeutic success. A therapy is therefore necessarily linked with increasing active substance tolerance.

Combination therapies should thus overcome the disadvantages linked with monotherapies.

WO 01/13903, for example, describes a combination of active substances contained, *inter alia*, in a TDS for the treatment of Restless Leg Syndrome, consisting of an α2 agonist and a further neuropsychological drug that reduces the symptoms of RLS in a monotherapy.

Mentioned, *inter alia*, as a neuropsychological drug of the group of dopamine agonists is S(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxy-tetraline (e.g. as N-0923) as a

component of the active substance combination. However, embodiment examples in this regard are lacking.

WO 01/13902 defines a combination of active substances *inter alia* for transdermal application, consisting of the α2 agonist clonidine and the dopamine agonist pramipexole for the treatment of Restless Leg Syndrome.

The embodiment examples in both documents describe the treatment of two patients using a combination therapy consisting of pramipexole and clonidine.

Pramipexole is fundamentally recognised for the treatment of sensorimotor RLS symptoms.

Tiredness, impaired digestion (dyspepsia), headaches and secretory congestion are reported as considerable further undesired effects (side effects) of this substance.

However, since the clonidine present in the combination of active substances – as suggested in the WO specifications – does not have an influence on the quality of sleep, the frequency of waking or periodic leg movements during sleep, the active substance clonidine therefore does not make an essential contribution to the alleviation of RLS.

As mentioned above, the α2 agonist clonidine is therefore only the second choice for the treatment of RLS.

This is confirmed by the US American Restless Leg Syndrome Foundation in its "RLS Medical Bulletin".

In the chapter entitled "Treatment", "secondary pharmacological treatments" are dealt with after "primary pharmacological treatments". "Secondary pharmacological treatments" are qualified therein as treatments that are not well-established or whose efficacy in treating RLS is limited.

In addition to other active substances, clonidine is also mentioned as not being sufficiently effective for the illness of RLS.

It is concluded that the use of clonidine for the treatment of RLS cannot be recommended with conviction. Patients would have to understand that evidence for the use of this substance is minimal.

Finally, treatment with the combination therapy as described in the two WO specifications cited above was only carried out on a total of 2 test persons (in each case one (1) male and one (1) female test person), and it is thus not possible to make any statements with regard to the therapy and the course thereof.

The proposed plaster formulations are also either cumbersome to handle, technically difficult to realise or economically cost-intensive.

If, as stated in the aforementioned WO specifications, the two active substances are each applied in a separate plaster, handling is laborious for the patient and there is no sufficient compliance. There is, *inter alia*, the danger of the plasters being confused and therefore that the patient will apply two (2) plasters having the same active substance.

If the two active substances are stored as a mixture in the same plaster, it cannot be ensured that the therapeutically required dose of each individual component will be able to have an effect. The required efficacy is thus not sufficiently ensured.

If the two active substances are stored separately in the plaster, the production of such a plaster is complex as regards design and cost-intensive.

Finally, the therapy of an illness should occur as far as possible with individual substances in order to keep interactions with other administered substances as low as possible. This therapeutic requirement is significant for RLS since this illness – as mentioned above – occurs with increased age when multi-morbidity often occurs.

A number of obstacles must be overcome in the case of RLS medication.

For example, when administering levodopa, only a limited and irregular absorption in the intestine, in particular the duodenum, is possible, and thus reproducible plasma levels cannot be achieved. This is particularly true if food is consumed at the same time.

Most of the active substances that can be used for the illness of RLS are subject to first-pass metabolism by the liver when administered orally.

These factors can result, in the case of oral administration, in a delayed and non-reproducible onset of effect and an unpredictable duration of effect. The fluctuating levodopa/plasma concentrations caused are particularly undesirable. Plasma concentration peak values often correlate with the occurrence of undesired side effects, however, if the

plasma level is too low, the effect abates. L-dopa must therefore be administered several times daily, which can lead to problems in compliance.

The disadvantages of oral administration cited above led to the search for other, more effective modes of administration for levodopa or other active substances against the illness of RLS. The following, non-oral modes of administration were considered: intravenous, transdermal, subcutaneous, intramuscular, intracerebroventricular, intranasal, pulmonary, sublingual or intrarectal.

However, none of these modes has, as yet, led to therapeutically satisfactory systems of administration or to therapy successes.

The proposed non-oral modes of administration in particular have the limitations that some of them are invasive and complications may occur. This was the case, for example, for the long-term intraduodenal administration of a levodopa solution. The exchange of the catheter tips in particular is often linked with wounds and pain.

Continuous intravenous or subcutaneous infusion is not therapeutically satisfactory either. Although stable plasma concentrations can be achieved, for example, with subcutaneously administered infusions of apomorphine, unacceptable local irritations occur if apomorphine has to be administered several times daily over a long period of time.

There was, and still is, therefore the need to provide an active substance for the therapy of RLS

- which is well-tolerated,
- which can be used as a monotherapy, and
- which is present in a pharmaceutical/technical formulation that meets the therapeutic requirements,

and

with which the active substance-containing formulation can be produced in a favourable manner in terms of both technology and costs aspects.

It has been surprisingly and unexpectedly found that a transepicutaneous form of administration containing rotigotine, in particular in the form of a TDS, is of therapeutic value for the treatment of RLS. This form of administration is therapeutically effective particularly for the treatment of RLS patients who are reliant upon a continuous long-term treatment of RLS symptoms and who are susceptible to RLS augmentation.

Description of the Invention

The present invention therefore relates to the use of rotigotine for the production of a pharmaceutical composition in the form of a transepicutaneous pharmaceutical preparation, in particular in the form of a transdermal therapeutic system (TDS), which avoids the disadvantages known from the prior art of current monotherapies with orally administered active substances.

It has surprisingly shown that the administration of rotigotine as an agent in monotherapy in a transepicutaneous composition, in particular in the form of the pharmaceutical composition of a TDS, causes the suppression and reduction of the symptoms of RLS, the active substance rotigotine, in contrast to monotherapies known to date, also being able to be administered in very low doses over a long period and being well tolerated.

The form of administration according to the invention is particularly suitable for the treatment of medium to severe RLS complaints.

Rotigotine is the INN (International Nonproprietary Name) of the chemical substance (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol.

The compound (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol is obtained in a manner known per se. The aforementioned compound is produced as described in EP 0 168 505 B1. Reference is herewith made to the entire scope thereof for the present invention.

It is already known that (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol can be used as a means for treating Parkinson's disease.

However, it is significant to note in this regard that the disorder RLS is not a form of Parkinson's disease but is rather a different illness hereto.

It has now been found that the administration of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in a transepicutaneous form of administration advantageously influences the illness of Restless Leg Syndrome.

The compound to be used according to the invention surprisingly displays a specific effect even at very low doses, which enables it to be used for the treatment of Restless Leg Syndrome. The compound is superior to the known substances effective for the indication

of Restless Leg Syndrome as regards both the strength of the effect and the specificity thereof.

Such an efficient and specific effect was not known to date in the number of agents against RLS for use in monotherapy known from the prior art, and thus the use of the compound in the form of administration according to the invention as a therapeutic agent for Restless Leg Syndrome represents an enrichment for pharmacy and medicine.

The form of administration according to the invention provides, in a therapeutically advantageous manner, constant plasma levels which avoids the pulsatile plasma levels occurring with oral forms of administration. There is, in particular, no food interaction as is known from L-dopa therapy, which has the consequence that plasma levels and therapeutic effects cannot be reproduced.

One advantage of the invention is that when using the active substance rotigotine in a transdermal application form for the treatment of Restless Leg Syndrome, low doses alone are sufficient to improve the condition of the patient without intolerable, undesired effects (side effects) thereby occurring; it is particularly important for augmentation to be suppressed. This is particularly desirable since in approximately half of the RLS patients with augmentation, a change in medication is necessary. Receptiveness and the response rates in patients with RLS were furthermore improved. The active substance is applied in an amount of 1.0 to 10 mg, preferably in an amount of 0.5 to 5 mg per day, which is particularly advantageous according to the invention.

A further advantage of the form of administration according to the invention is due to the comfortable provision of the active substance rotigotine over at least 24 hours with constant plasma levels.

The active substance is applied to the patient's skin in the form of a transepicutaneous application either as a salve, gel or cream, however it is preferably administered as a TDS in the form of a plaster.

According to the invention, the transdermal therapeutic system has a backing layer that is inert with respect to the components of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and a protective film to be removed before use, characterised in that said matrix layer

a) contains, as the base, a non-aqueous acrylate or silicone-based polymer adhesive,

b) has a solubility of ≥ 5 % (g/g) for the free base (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and

c) contains the free base (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in an effective amount.

According to a further development, the matrix of the TDS contains < 0.5 % (g/g) of inorganic silicate particles.

According to a particularly advantageous further development, the transdermal therapeutic system contains < 0.05 % (g/g) of inorganic silicate particles in the matrix.

According to one embodiment of the invention, the transdermal system contains an acrylate-based polymer adhesive comprising at least two of the following monomers:

acrylic acid, acrylamide, hexyl acrylate, 2-ethyl hexyl acrylate, hydroxyethyl acrylate, octyl acrylate, butyl acrylate, methyl acrylate, glycidyl acrylate, methacrylate acid, methacrylamide, hexyl methyl acrylate, 2-ethyl hexyl methacrylate, octyl methacrylate, methyl methacrylate, glycidyl methacrylate, vinyl acetate or vinyl pyrrolidone.

According to an advantageous further development of the invention, the transdermal system comprises a silicone-based polymer adhesive with additives for improving the solubility of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in the form of hydrophilic polymers or glycerine or glycerine derivatives.

According to a further embodiment according to the invention, in the transdermal system, (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol is contained in the acrylate-based polymer adhesive in a concentration of 10 to 35 % [g/g] or in the silicone-based polymer adhesive in a concentration of 5 to 40 % [g/g].

According to another further development of the invention, the transdermal system contains substances that improve the permeation of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol into human skin.

According to the invention, the permeation-promoting substance for the transdermal system is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerine or derivatives thereof, N-methyl pyrrolidone, terpenes or terpene derivatives.

According to an embodiment of the invention, the permeation-promoting substance in the transdermal therapeutic system is oleic acid or oleyl alcohol.

According to the invention, the hydrophilic polymer in the transdermal system is advantageously polyvinyl pyrrolidone, a copolymer of vinyl pyrrolidone and vinyl acetate, polyethylene glycol, polypropylene glycol or a copolymer of ethylene and vinyl acetate.

In a further embodiment, the hydrophilic polymer in the transdermal system is contained in the active substance-containing matrix layer in the form of soluble polyvinyl pyrrolidone and at a concentration of 1.5 to 5 % (g/g).

According to the invention, the transdermal system can furthermore contain inert fillers in the matrix for improving cohesion.

The transdermal therapeutic system can be produced as described in detail in the embodiment examples of EP 1 033 978 B1.

A pharmaceutical product according to the present invention comprises a backing layer that is inert with respect to the components of the matrix, a self-adhesive matrix layer comprising an effective amount of rotigotine or rotigotine hydrochloride, and a protective film that is to be removed before use.

Embodiment Example 1

Polyacrylate system with (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)-ethyl]-amino]-1-naphthol

66 g of a 50 % solution of Eudragit E100 in ethyl acetate are added to 264 g of a solution of a polyacrylate adhesive with a solids content of 50 %, and following the addition of 36g of oleyl alcohol, the mass is homogenised by stirring.

89.65 g of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol are then dissolved in 200 ml of methyl ethyl ketone and are added to the above mass whilst being stirred. Once the mass is homogenised, it is coated onto a siliconised polyester film using a suitable doctor blade. The thickness of the moist film is to be dimensioned such that following removal of the solvent by means of drying for 30 minutes at 50 °C, a coating weight of 60 g/m^2 results.

The dried matrix film is now laminated with a 13 μm thick polyester film. The finished plasters are now punched out of the resulting plaster laminate at the desired size and are packed in packaging bags.

The concentration of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in the plaster matrix is 30.8 %. Suitable polyacrylate adhesives are, for example, Durotak 387-2051, Durotak 387-2287, Durotak 387-2353 and Durotak 387-2516, all by National Starch & Chemical.

Embodiment Example 2

Silicone system with (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)-ethyl]-amino]-1-naphthol

18 g of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol dissolved in 40 g of ethanol are added to 24 g of a 25 % solution of Kollidon 90F and the mass is homogenised. 251 g of a solution of an amine-resistant silicone adhesive having a solids content of 70 % is subsequently added to this mass and the mass is homogenised by means of further stirring.

The mass is then coated onto a polyester film provided with an adhesive (Scotchpak 1022) using a suitable doctor blade at a thickness resulting in a coating weight of 50 g/m^2 following removal of the solvent by means of drying for 30 minutes at 50 °C.

The dried matrix film is now laminated with a 13 μm thick polyester film. The finished plasters are punched out of the resulting plaster laminate at the desired size and are packed in packaging bags.

The concentration of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol base in the plaster matrix is 9 %.

Suitable amine-resistant silicone adhesives are, for example, BIO-PSA Q7-4301 and BIO-PSA Q7-4201, both by Dow Corning.

Embodiment Example 3

25 g of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol hydrochloride are stirred together with 14.7 g of sodium metasilicate or 16.8 g of sodium trisilicate in 40 ml of ethanol at room temperature for 48 hours. The active substance

solution is now optionally filtrated and 9.2 g of oleyl alcohol, 63.2 g of a 52 % solution of a polyacrylate adhesive (Durotak 387-2287 of the firm National Starch & Chemical) and 22.8 g of a 40 % (g/g) solution of Eudragit E100 (Röhm-Pharma) are added and the mass is subsequently homogenised by means of mechanical stirring.

The mass is subsequently coated onto a suitable polyester film provided with an adhesive in order to produce the plaster matrix and the solvent is removed by means of drying for 20 minutes at 50 °C. The coating weight of the dried matrix film is 80 g/m².

The dried matrix film is laminated with a 23 μm thick polyester film. The individual plasters are punched out of the completed laminate.

According to the invention, it is finally exceptionally advantageous to use a silicone-based transdermal therapeutic system that must contain at least one amine-resistant silicone compound as the main component.

The silicone compound is normally a pressure-sensitive adhesive or a mixture thereof and forms a matrix in which the other components of the TDS are embedded. Furthermore, the adhesive(s) should preferably be pharmaceutically acceptable such that they are biocompatible, non-sensitising and non-irritating to skin. Particularly advantageous silicone adhesives for the use according to the invention should furthermore meet the following requirements:

- lasting adhesive and cohesive properties in the presence of moisture or perspiration within normal temperature fluctuations,

- good compatibility with rotigotine as well as with the other carriers used in the formulation, in particular the adhesive should not react with the amine group of rotigotine.

It has been shown that pressure-sensitive adhesives of the type forming a soluble polycondensated polydimethyl siloxane (PDMS) / resin network, the hydroxy end groups being capped, for example, by trimethylsilyl (TMS) groups, are particularly useful according to the invention. Preferred adhesives of this type are the BIO-PSA pressure-sensitive silicon adhesives produced by Dow Corning, in particular the Q7-4201 and Q7-4301 qualities. Other silicone adhesives can, however, likewise be used.

In addition and preferably, a silicon-based transdermal therapeutic system is also provided according to the invention for the same use, which comprises two or more silicone resins

as adhesive main components. It can be advantageous for such a mixture of silicone adhesives to comprise at least one high tack adhesive and at least one medium tack adhesive in order to ensure an optimal balance between good adhesion and low cold flux. Excessive cold flux can lead to too soft a plaster that easily adheres to the packaging or to the patient's clothes. Such a mixture of adhesives furthermore seems to be particularly useful in order to obtain an effective transdermal therapeutic system. A mixture of the aforementioned amine-resistant pressure-sensitive silicone adhesives Q7-4201 (medium tack) and Q7-4301 (high tack) in approximately equal amounts has proven to be particularly useful according to the invention.

In a further preferred embodiment, the silicone-based transdermal therapeutic system comprises a solubiliser. Different surfactant-like or amphiphilic substances may be used as solubilisers. They should be pharmaceutically acceptable and approved for use in medicaments. It is advantageous if the solubiliser also causes an improvement in the cohesion of the transdermal therapeutic system. A particularly preferred example of such a solubiliser is soluble polyvinyl pyrrolidone. Polyvinyl pyrrolidone is commercially available, for example under the trademark name Kollidon® (Bayer AG). Other examples include copolymers of polyvinyl pyrrolidone and vinyl acetate, polyethylene glycol, polypropylene glycol, glycerine and fatty acid esters of glycerine or copolymers of ethylene and vinyl acetate.

The silicone-based transdermal therapeutic system contains less than 1 % by weight of inorganic silicates for the use according to the invention, it is most preferred for it to be completely free of inorganic silicates.

The water content of the transdermal therapeutic system for the use according to the invention is preferably so low that evaporation of water is not necessary during the production of the TDS. The water content of a newly made plaster is typically less than 2% by weight and is preferably 1 % by weight or less.

In a particularly preferred embodiment according to the invention, the transdermal therapeutic system has a surface area of 10 to 30 cm^2, preferably 5 to 20 cm^2. It goes without saying that a TDS having a surface area of, for example, 20 cm^2 is pharmacologically equivalent to and can be interchanged with two 10 cm^2 plasters or four 5 cm^2 plasters having the same amount of medicament per cm^2. The surface areas specified in this application are therefore to be understood as relating to the total surface of all TDS simultaneously applied to a patient.

The provision and application of one or more transdermal therapeutic systems according to the invention has the pharmacological advantage over an oral therapy that the responsible doctor can titrate the optimum dose for the patient comparatively quickly, individually and accurately, e.g. by simply increasing the number or size of the plasters to be given to the patient.

If a seven-day plaster is desired, higher amounts of medicament are generally necessary. It was found that a rotigotine content in the range of approximately 0.4 to 0.5 % by weight is particularly advantageous since it optimally uses the medicament contained in the TTS, i.e. the amount of medicament remaining in the TTS following administration is only very low. The dose administered using such a TTS is normally 50 % or more of the amount of medicament originally contained in the TTS, and can be as high as 80 to 90 %.

The fact that the silicone-based transdermal therapeutic system described according to the invention causes a significant therapeutic effect on the symptoms of Restless Leg Syndrome even with surface areas of 10 to 20 cm^2, in particular of less than 10 cm^2, and with low amounts of medicament of approximately 0.4 to 0.5 mg/cm^2, in particular 0.45g/cm^2, must be seen as a further advantage of the invention.

The transdermal therapeutic system used according to the invention is preferably a plaster with a continuous adhesive matrix containing the medicament at least in its central part. However, transdermal equivalents to such plasters are also comprised by the invention, i.e. an embodiment in which the medicament is disposed in an inert but non-adhesive silicone matrix in the central part of the TTS and an adhesive part extends along the ends of the plaster.

The invention furthermore relates to a process for treating the RLS, wherein a transdermal therapeutic system having a surface area of 5 to 20 cm^2 is applied to a patient.

The invention and the best embodiment will be described in more detail below.

Embodiment Example 4

A transdermal therapeutic system using a combination of pressure-sensitive silicone adhesives was prepared as follows.

(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthalenol hydrochloride (rotigotine hydrochloride, 150 g) was added to a solution of 17.05 g NaOH in 218 g of ethanol (96 %). The resulting mixture was stirred for approximately 10 minutes. 23.7 g of

sodium phosphate buffer solution (8.35 g of $Na_2HPO_4x2H_2O$ and 16.07 g of $NaH_2PO_4x2H_2O$ in 90.3 g of water) were then added. Insoluble or precipitated substances were separated from the mixture by means of filtration. The filtrate was washed with 60.4g of ethanol (96 %) in order to obtain a particle-free ethanol solution of rotigotine in free base form.

The solution of rotigotine in free base form (346.4 g) in ethanol (35 % G/G) was mixed with 36.2 g of ethanol (96 %). The resulting solution was mixed until homogeneous with 109 g of an ethanol solution containing 25 % by weight of polyvinyl pyrrolidone (KOLLIDON® 90F), 0.077 % by weight of liquid sodium bisulphite solution (10 % by weight), 0.25 % by weight of ascorbyl palmitate and 0.63 % by weight of DL alpha tocopherol. 817.2 g of an amine-resistant, high tack silicone adhesive (BIO-PSA® Q7-4301, produced by Dow Corning) (74 % by weight solution in heptane), 851.8 g of an amine-resistant medium tack silicone adhesive (BIO-PSA® Q7-4201, produced by Dow Corning) (71 % by weight solution in heptane) and 205.8 g of petrol ether (heptane) were added to the mixture and all of the components were stirred until a homogeneous dispersion was obtained.

The dispersion was applied to a suitable polyester release lining (SCOTCHPAK® 1022) using a suitable doctor blade and the solvents were continuously removed in a drying oven at temperatures of up to 80 °C for approximately 30 minutes and a medicament-containing adhesive matrix having a coating weight of 50 g/m² was thus obtained. The dried matrix film was laminated with a polyester-type backing film (SCOTCHPAK® 1109). The individual plasters were punched out of the completed laminates at the desired sizes (e.g. 5 cm², 10 cm², 20 cm², 30 cm²) and were sealed in bags under the flow of nitrogen.

The following table shows the composition in mg/20 cm² of a transdermal therapeutic system according to the invention, which contains a combination of silicon-type PSA.

Components of the composition	Amount (mg)
Rotigotine base	9.00
Polyvinyl pyrrolidone	2.00
Silicone BIO-PSA® Q7-4301	44.47
Silicone BIO-PSA® Q7-4201	44.46
Ascorbyl palmitate	0.02
DL alpha tocopherol	0.05
Sodium metabisulphite	0.0006
Coating weight of the matrix	50 g/m²

Clincal Tests

The rotigotine TDS produced according to embodiment example 4 was examined in placebo-controlled, double-blind, randomised clinical tests at several centres and included, in a three-armed study with parallel groups, 63 patients suffering from medium to very severe idiopathic illnesses of Restless Leg Syndrome.

The average age of the patients was 58.3 years old. Randomisation in the three treatment groups was adequately balanced as regards gender, age and severity of prior illnesses.

The patients were treated with rotigotine TDS following gradual and complete termination of the current therapy with L-dopa and a break in therapy (washout) of 7 ± 4 days.

Over the treatment period of eight (8) days, the patients of one group were treated with 5cm² TDS and the patients of another group were treated with 10 cm² TDS. By way of comparison, the patients in the placebo group were treated with placebo TDS. All of the groups received 4 plasters as a combination of verum and placebo plasters. The first group, for example, received a combination of two 2.5 cm² verum plasters and two placebo plasters and the second group received four 2.5 cm² verum plasters. The placebo group received four placebo plasters. A 2.5 cm² TDS comprised a rotigotine amount of 1.125 mg. 5 cm² therefore contained a rotigotine amount of 2.25 mg and a 10 cm² TDS contained 4.5 mg. Approximately 50 % of the active substance (apparent dose) rotigotine was released to the individual patients from the respective aforementioned active substance-containing TDS within 24 hours.

It was found that an effective alleviation of the symptoms of Restless Leg Syndrome in patients suffering from this illness was achieved after just one (1) week. The patients were not receiving any other medicaments effective against RLS at this point.

As a result of the prespecified primary effectiveness, the activities of daily life and motoricity changed, in accordance with the generally accepted International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, between the initial value and the final treatment evaluation (8th day).

The IRLSSG measures and categorises the following clinical parameters in patients with Restless Leg Syndrome on the basis of 10 questions.

1. Overall, how would you rate the RLS discomfort in your arms or legs?

0 = none = no symptoms
1 = mild
2 = moderate
3 = considerable
4 = very severe symptoms

2. Overall, how would you rate the need to move around because of your RLS symptoms?

0 = none
1 = mild
2 = moderate
3 = considerable
4 = high

3. Overall, how much relief from your RLS arm or leg discomfort did you get from moving around?

0 = no RLS discomfort had to be relieved
1 = complete or almost complete
2 = moderate
3 = slight
4 = none

4. How severe was your sleep disturbance due to your RLS symptoms?

0 = none
1 = mild
2 = moderate
3 = considerable
4 = high

5. How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

0 = none
1 = mild
2 = moderate
3 = considerable

4 = severe

6. How severe was your RLS as a whole?

0 = none
1 = mild
2 = moderate
3 = considerable
4 = severe

7. How often do you get RLS symptoms?

0 = never
1 = occasionally (i.e. 1 out of the last 7 days)
2 = sometimes (i.e. 2 to 3 out of the 7 days)
3 = often (i.e. 4 to 5 out of the last 7 days)
4 = very often (i.e. 6 to 7 out of the last 7 days)

8. When you had RLS symptoms, how severe were they on average?

0 = none
1 = mild (i.e. for less than 1 hour in a 24 hour period)
2 = moderate (i.e. for 1 to 3 hours in a 24 hour period)
3 = considerable (i.e. for 3 to 8 hours in a 24 hour period)
4 = severe (i.e. for 8 or more hours in a 24 hour period)

9. Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example leading a satisfactory family, private, academic or work life?

0 = none
1 = mild
2 = moderate
3 = considerable
4 = high

10. How severe was your mood disturbance due to your RLS symptoms – for example, were you angry, depressed, sad, anxious or irritable?

0 = none
1 = mild
2 = moderate
3 = considerable
4 = severe

The overall IRLSSG rating is determined from the individual values as follows:

An initial value for each patient participating in the study is first of all determined. This is namely done by adding together the individual IRLSSG parameter values on day 0, i.e. before the treatment. The IRLSSG values during the course of the treatment are then compared with this initial value and changes with regard to the initial value are recorded. Finally, the average improvement of the IRLSSG value on day 8 as compared to the initial value is determined by taking the average of all the test persons. The resulting value is referred to as the FAS (full analysis set) randomised average change from the initial value of the overall IRLSSG rating. The expression "randomised" indicates that the patients were randomised in advance in a double-blind manner as regards the different prespecified doses.

Patients suffering from the illness of Restless Leg Syndrome have been known to experience a relatively strong placebo effect, i.e. even in the case of placebo treatment the IRLSSG values of patients with restless leg syndrome improve to a certain extent. It is therefore important to compare any effect of the medicament treatment with the assessment of the IRLSSG improvement achieved with a placebo treatment over the same period. The final evaluation of the improvement is therefore carried out in relation to the effect of a placebo treatment over the same period.

Results

There was a significant, dosage-related improvement in the IRLSSG values between the initial value and that 8 days after the application of a TDS according to the invention. As compared to the placebo group, in particular the group treated with a TDS having a rotigotine amount of 4.5 mg (apparent dose 2.25 mg) exhibited therapeutically particularly favourable IRLSSG values. This result can be seen from the following table.

Size of the plaster (TDS)	Amount of rotigotine	Reduction of the average IRLSSG value as compared to the placebo treatment on day 8	p (one-sided)
5 cm^2	2.25 mg	3.6	0.09
10 cm^2	4.5 mg	6.3	0.04

The value referred to as "p" in the above table represents the one-sided p value obtained by the statistical assessment of the test data.

At the end of the eight-day treatment, both patient groups reported that almost all of the subjective symptoms such as prickling, cramps, pain in the legs, restlessness of the legs during the night and problems in falling asleep or staying asleep, no longer existed or had been reduced to a tolerable minimum such that their quality of daily life was no longer negatively affected.

Depending on the administered dose of the active substance rotigotine, patients furthermore reported that they only suffered very mildly from or did not suffer at all from tiredness during the day, no nausea, dizziness, vomiting or sleeplessness, etc.

Rotigotine was generally well tolerated when administered using the TDS according to the invention.

Skin reactions at the site of application were generally very mild.

Conclusions

The above results show for the first time in a double-blind placebo-controlled study that a dopamine agonist (rotigotine) administered transdermally once daily leads to a clear clinical improvement in patients with Restless Leg Syndrome at medium to severe stages and is well tolerated. An advantage of this medication could be ascertained particularly in patients whose RLS symptoms occurred more intensely during the day.

It was not possible to date to achieve such a result with orally administered medicaments in a monotherapy, whereby even an improvement in the IRLSSG value of 2 as compared to the placebo can be considered a success. An improvement by over 3 or 6 or more units therefore constitutes an even greater therapeutic advance and is thus preferred according to the invention.

Long-Term Study

A long-term study over four (4) months or 120 days was carried out retaining the aforementioned clinical examination model.

Rotigotine TDS produced according to embodiment example 4 were again used.

The study was carried out in a placebo-controlled, double-blind and randomised manner as a three-armed study with parallel groups with twelve (12) patients suffering from medium to very severe idiopathic complaints of Restless Leg Syndrome.

The average age of the patients was 60 years old. Randomisation in the three treatment groups was adequately balanced as regards gender, age and severity of prior illnesses.

The patients were treated with rotigotine TDS following gradual and complete termination of the current therapy with L-Dopa and a break in therapy (washout) of 8 ± 4 days.

Over the treatment duration of four (4) months, the patients of one group were treated with 5 cm^2 TDS, the patients of another group were treated with 10 cm^2 TDS and by way of comparison, the patients in the placebo group were treated with placebo TDS. 5 cm^2 TDS had a rotigotine amount of 2.25 mg and 10 cm^2 TDS had an amount of 4.5 mg. 50 % of the active substance (apparent dose) rotigotine was released to the individual patients from the respective aforementioned active substance-containing TDS within 24 hours.

It was found that an effective alleviation of the symptoms of Restless Leg Syndrome in patients suffering from this illness was achieved after just one (1) week. The patients were not receiving any other medicaments effective against RLS at this point.

As a result of the prespecified primary effectiveness, the activities of daily life and motoricity changed, in accordance with the generally accepted International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, between the initial value and the final treatment evaluation (120^{th} day).

The IRLSSG measures – as described above – and categorises the clinical parameters in patients with Restless Leg Syndrome on the basis of 10 questions.

Results

There was a significant, dose-related improvement in the IRLSSG values between the initial value and that 120 days after the application of a TDS according to the invention. As compared to the placebo group, in particular the group treated with a TDS having a rotigotine amount of 4.5 mg (apparent dose 2.25 mg) exhibited therapeutically particularly favourable IRLSSG values.

At the end of the 120 day treatment, both patient groups reported that all of the subjective symptoms and the problems in falling asleep or staying asleep no longer existed or had been reduced to a minimum such that their quality of daily life was no longer negatively affected. There was no significant augmentation. The IRLSSG value in the group treated with a TDS having 2.25 mg of rotigotine was 12.8 and was 15.7 in the group treated with a TDS having 4.5 mg of rotigotine.

Depending on the administered dose of the active substance rotigotine, patients furthermore reported that over the course of the treatment they only suffered very mildly from or did not suffer at all from tiredness during the day, no nausea, dizziness, vomiting or sleeplessness, etc.

Rotigotine was generally well tolerated when administered using the TDS according to the invention.

Skin reactions at the site of application were generally very mild. Where necessary TDS was applied at a different site on the skin. The previous site of application recovered quickly and could be used for a further treatment.

Conclusions

The above results show for the first time in a double-blind placebo-controlled long-term study that a dopamine agonist (rotigotine) administered transdermally once daily is well tolerated and safe and causes a significant clinical improvement in patients with Restless Leg Syndrome at a medium to severe stage.

It was not possible to date to achieve such a result with orally administered medicaments in a monotherapy, however even an improvement in the IRLSSG value of 2 as compared to the placebo can be considered a success. An improvement by 10 or more units therefore constitutes an even greater therapeutic advance and is thus preferred according to the invention.

The study particularly shows the effectiveness of the form of administration according to the invention in alleviating the illness in patients suffering from RLS, in whom an increase in RLS complaints owing to different earlier medication could be observed.

New Patent Claims

1. Use of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol for the production of a medicament for the transepicutaneous treatment of Restless Leg Syndrome.

2. Use according to claim 1, characterised in that the medicament is suitable for applying 0.5 to 10 mg of active substance per day.

3. Use according to claim 1 or 2, wherein the medicament is a transdermal therapeutic system (TDS) comprising a backing layer that is inert with respect to the components of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and a protective film to be removed before use, characterised in that said matrix layer

   a) contains, as the base, a non-aqueous acrylate or silicone-based polymer adhesive,

   b) has a solubility of ≥ 5 % (g/g) for the free base (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and

   c) contains the free base (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in an effective amount.

4. Use according to claim 3, characterised in that the matrix contains < 0.5 % (g/g) of inorganic silicate particles.

5. Use according to claim 3, characterised in that the matrix contains < 0.05 % (g/g) of inorganic silicate particles.

6. Use according to claim 3, in which the acrylate-based polymer adhesive comprises at least two of the following monomers:

   acrylic acid, acrylamide, hexyl acrylate, 2-ethyl hexyl acrylate, hydroxyethyl acrylate, octyl acrylate, butyl acrylate, methyl acrylate, glycidyl acrylate, methacrylate acid, methacrylamide, hexyl methyl acrylate, 2-ethyl hexyl methacrylate, octyl methacrylate, methyl methacrylate, glycidyl methacrylate, vinyl acetate or vinyl pyrrolidone.

7. Use according to claim 3, in which the silicone-based polymer adhesive contains additives for improving the solubility of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol in the form of hydrophilic polymers or glycerine or glycerine derivatives.

8. Use according to claim 6 or 7, in which (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol is contained in the acrylate-based polymer adhesive in a concentration of 10 to 35 % [g/g] or in the silicone-based polymer adhesive in a concentration of 5 to 40 % [g/g].

9. Use according to claim 8, wherein the TDS contains substances that improve the permeation of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol into human skin, selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerine or derivatives thereof, N-methyl pyrrolidone, terpenes or terpene derivatives.

10. Use according to claim 9, in which the permeation-promoting substance is oleic acid or oleyl alcohol.

11. Use according to claim 7, in which the hydrophilic polymer is polyvinyl pyrrolidone, a copolymer of vinyl pyrrolidone and vinyl acetate, polyethylene glycol, polypropylene glycol or a copolymer of ethylene and vinyl acetate.

12. Use according to claim 11, in which the hydrophilic polymer is soluble polyvinyl pyrrolidone and is contained in a concentration of 1.5 to 5 % (g/g) in the active substance-containing matrix layer.

13. Use according to claim 3, wherein the TDS comprises a mixture of at least one high tack silicone adhesive and at least one medium tack silicone adhesive.

14. Use according to claim 13, wherein the TDS further comprises a solubiliser.

15. Use according to claim 16, wherein the solubiliser is (soluble) polyvinyl pyrrolidone.

17. Use according to one of claims 13 to 16, wherein the TDS contains less than 1 % by weight of inorganic silicates.

18. Use according to claim 17, wherein the TDS is free from inorganic silicates.

19. Use according to claim 3, wherein the TDS has a size of 5 to 20 cm^2 and contains 0.4 to 0.5 mg/cm^2 of rotigotine as the active component in its matrix, which primarily comprises a mixture of at least two amine-resistant silicone adhesives.

20. Use of a silicone-based transdermal therapeutic system having a surface area of 5 to 20 cm^2 and containing 0.1 to 3.15 mg/cm^2 of rotigotine as the active component for the production of an anti-Restless Leg Syndrome medicament which, in accordance with the International Restless Leg Syndrome Study Group Rating Scale (IRLSSG), leads to an improvement of 2 units or more in human patients suffering from Restless Leg Syndrome as compared to a placebo treatment after at least eight days of application.

21. Method for the treatment of Restless Leg Syndrome by applying a transdermal therapeutic system having a surface area of 5 to 20 cm^2 and containing 0.1 to 3.15mg/cm^2 of rotigotine as the active component to a patient suffering from this illness, which, in accordance with the Restless Leg Syndrome Study Group Rating Scale, leads to an improvement in the condition of the patient of approximately 2 units or more as compared to a placebo treatment after a period of 8 days.